

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 03761WONL	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/HU2004/000026	International filing date (day/month/year) 23.03.2004	Priority date (day/month/year) 24.03.2003	
International Patent Classification (IPC) or national classification and IPC C07D207/34, A61K31/00, A61P3/06			
Applicant RICHTER GEDEON VEGYESZETI GYAR RT. et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 1 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 07.10.2004		Date of completion of this report 08.11.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Menegaki, F Telephone No. +49 89 2399-8277	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/HU2004/000026

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-7 as originally filed

Claims, Numbers

1 as amended (together with any statement) under Art. 19 PCT

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/HU2004/000026

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1
	No: Claims	
Inventive step (IS)	Yes: Claims	1
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/HU2004/000026

(V)

The Applicant has submitted new Claim 1 by introducing original Claim 3 into the original definition of Claim 1, supported by the original disclosure.

Having regard to the International Search Report as well as the prior art cited by the Applicant in the description, the claimed process for the preparation of amorphous atorvastatin calcium salt, starting from atorvastatin basic amino acid salts can be regarded as novel over the processes disclosed in documents

(D1) WO 01/28999; (D2) WO01/42209.

It is further noted that document (D3) WO 03/082816, a P-document not relevant at this stage, discloses atorvastatin basic amino acid salts per se, without reference to further processing to give the calcium salts.

The requirements of Art.33(2) PCT appear to be fulfilled.

The problem to be solved by the present invention is considered to be the provision of a process for the synthesis of amorphous atorvastatin calcium, which consists of dissolving atorvastatin basic amino acid salts of formula (I) in a mixture of water **and a water miscible organic solvent**, which the Applicant has now specified in new Claim 1 by introducing the definition of original Claim 3, subsequently adding an aqueous solution of a water soluble calcium salt, and isolating the precipitating amorphous atorvastatin calcium by filtration.

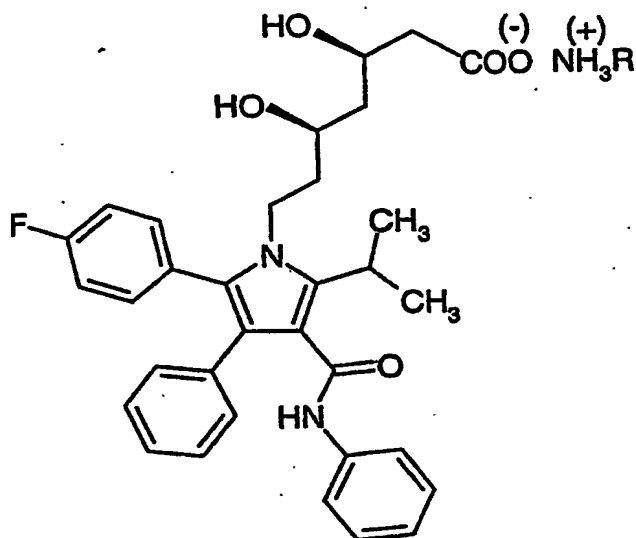
(D1) discloses a process for the preparation of amorphous atorvastatin-Calcium salt by recrystallization of crude atorvastatin, involving similar solvents under heating.

(D2) discloses a process for the conversion of atorvastatin-Ca of crystalline form (I) into atorvastatin-Ca in an amorphous form, by dissolving first atorvastatin-Ca (I), i.a. in an alkanol, and then precipitating by adding a solvent such as ether or aliphatic hydrocarbons.

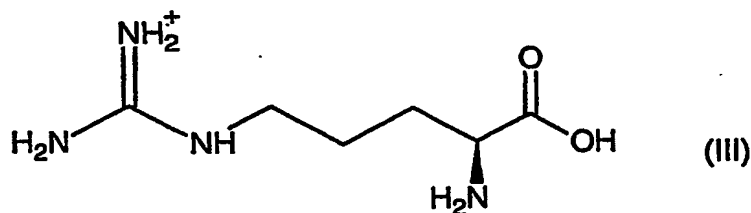
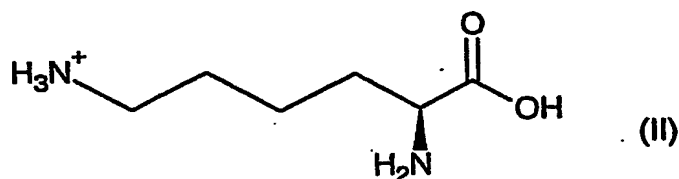
The present process, involving solution without heating, can therefore be regarded as inventive per se, in view of the specified definition of "water miscible organic solvent" in new Claim 1, in which the atorvastatin basic amino acid salts (I) are soluble and the subsequently resulting atorvastatin-Calcium salt insoluble.

The requirements of Art.33(3) PCT appear to be fulfilled for the present Claim 1, whereas the Applicant has withdrawn both original Claims 2 and 3 with his letter of 22/09/2004.

A process for the synthesis of amorphous atorvastatin calcium characterized by dissolving the salt of the formula (I) of atorvastatin acid formed with a basic amino acid



– wherein the meaning of R is the compound of formula (II) or (III)



- in a mixture of water and methanol, ethanol, isopropanol or acetone, adding an aqueous solution of a water soluble calcium salt to the solution and isolating the so obtained entirely amorphous atorvastatin calcium of high purity by filtration.

AMENDED SHEET (ARTICLE 19)